

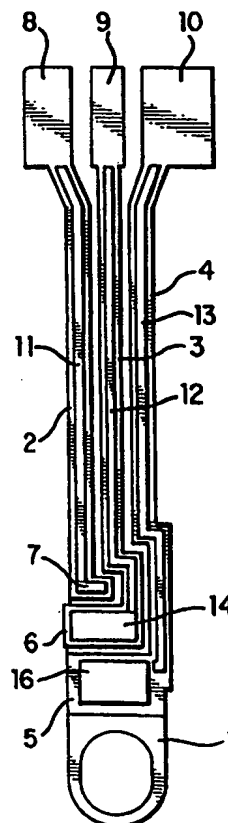


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/00, G01N 27/30, 27/327	A1	(11) International Publication Number: WO 99/19507 (43) International Publication Date: 22 April 1999 (22.04.99)
(21) International Application Number: PCT/US98/21815 (22) International Filing Date: 16 October 1998 (16.10.98) (30) Priority Data: 60/061,982 16 October 1997 (16.10.97) US (71) Applicant (for all designated States except US): ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ✓ FORROW, Nigel, J. [GB/GB]; 6 Grundy Close, Abingdon, Oxon OX14 3SD (GB); SANGHERA, Gurdial, S. [GB/US]; 4A Crosby Drive, Bedford, MA 01730 (US). WATKIN, Jared, L. [GB/GB]; 11 Kysbie Place, Abingdon, Oxfordshire OX14 1XZ (GB). ✓ WALTERS, Stephen [GB/GB]; Flat 4, Stanmore Road, Edgebaston, Birmingham B16 9TB (GB). (74) Agents: POPE, Lawrence, S. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: BIOSENSOR ELECTRODE MEDIATORS FOR REGENERATION OF COFACTORS**(57) Abstract**

The present invention is based on the discovery of NAD⁺ and NADP⁺ mediator compounds that do not bind irreversibly to thiol groups in the active sites of intracellular dehydrogenase enzymes. Such mediator compounds avoid a common mode of enzyme inhibition. The mediators can therefore increase the stability and reliability of the electrical response in amperometric electrodes constructed from NAD- or NADP-dependent enzymes.

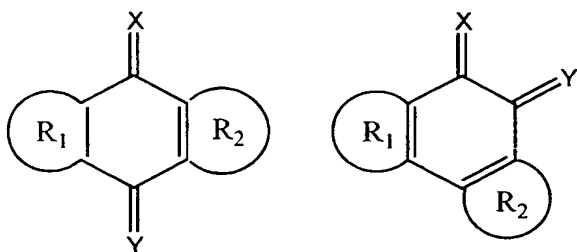


FOR THE PURPOSES OF INFORMATION ONLY

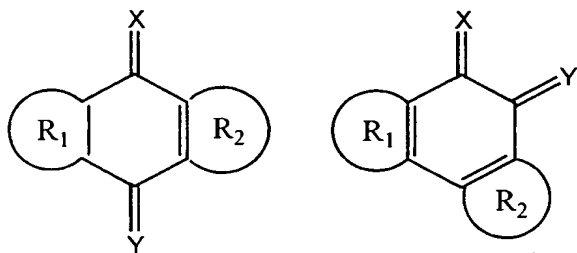
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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EE	Estonia	LR	Liberia	SG	Singapore		

In another embodiment, the invention features an electrode strip for an amperometric sensor having a readout. The strip includes a support adapted for releasable attachment to the readout, a first conductor extending along the support and comprising a conductive element for connection to the readout; a working electrode in contact with the first conductor and positioned to contact a sample mixture; a second conductor extending along the support and comprising a conductive element for connection to the readout; and a reference/counter electrode in contact with the second conductor and positioned to contact the sample and the second conductor. The active electrode of the strip includes a mediator compound having one of the formulae:



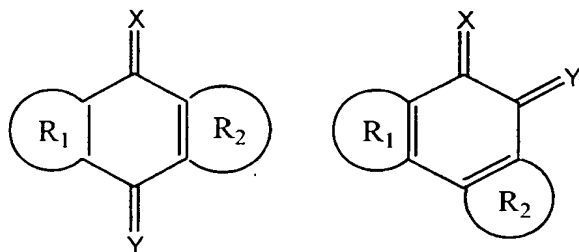
Still another embodiment of the invention features a method for mediating electron transfer between an electrode and a nicotinamide cofactor. The method includes the steps of using a mediator compound in the presence of a nicotinamide cofactor-dependent enzyme, where the mediator compound is a quinoid compound that is incapable of binding irreversibly to the thiol groups. The mediator compound can, for example, have reactive unsaturated bonds in adjacent aromatic ring. Suitable mediator compounds include those having the formulae:



For example, the mediator compound can be 1,10-phenanthroline quinone, 1,7-phenanthroline quinone, or 4,7-phenanthroline quinone.

Replicate by AMM
 by SP47703

In yet another embodiment, the invention features a printing ink. The ink includes a nicotinamide cofactor-dependent enzyme, a nicotinamide cofactor, and a mediator compound having one of the formulae:



For example, the mediator compound can be 1,10-phenanthroline quinone, 1,7-phenanthroline quinone, or 4,7-phenanthroline quinone. The enzyme can be, for example, alcohol dehydrogenase, lactate dehydrogenase, 3-hydroxybutyrate dehydrogenase, glucose-6-phosphate dehydrogenase, glucose dehydrogenase, formaldehyde dehydrogenase, malate dehydrogenase, or 3-hydroxysteroid dehydrogenase.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described below. All publications, patent applications, patents, technical manuals, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present application, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

An advantage of the new mediators is their non-reactivity with respect to active-site thiol groups in enzymes. This improves the stability and the shelf life of biosensor electrodes to an unexpected degree. Also as a result of this stability, the enzyme and mediator can be incorporated together in a printing ink or dosing solution to facilitate construction of the biosensors. The use of a mediator that is not an irreversible inhibitor of the enzyme will result in the retention of a large proportion of

that these chemically active ingredients remain in the immediate vicinity of the surface of the electrode. The binder ingredient should include materials which readily increase the viscosity of aqueous media and promote the formation of films or layers. Typical of such materials are the polysaccharides such as guar gum, alginate, locust
5 bean gum, carrageenan and xanthan. Also helpful are materials commonly known as film formers such as polyvinyl alcohol (PVA), polyvinyl pyrrole, cellulose acetate, carboxymethyl cellulose and poly (vinyl oxazolidinone). The filler ingredient should be a particulate material which is chemically inert to the oxidation reduction reactions involved in the measurement and insoluble in aqueous media. It may be electrically
10 conductive or non-conductive. Typical materials include carbon, commonly in the form of graphite, titanium dioxide, silica and alumina.

The active electrode may be conveniently produced by formulating the enzyme, cofactor, mediator and binder and filler ingredients into an aqueous vehicle and applying it to the elongated, electrically insulating carrier having conducting
15 tracks. The formulation may be applied by printing such as screen printing or other suitable techniques. The formulation may also include other ingredients such as a buffer to protect the enzyme during processing, a protein stabilizer to protect the enzyme against denaturation and a defoaming agent. These additional ingredients may also have an effect on the properties of the reaction layer.

20 The working electrode typically has a dry thickness between about 2 and 50 microns preferably between about 10 and 25 microns. The actual dry thickness will to some extent depend upon the application technique used to apply the ingredients which make up the working electrode. For instance thicknesses between about 10 and 25 microns are typical for screen printing.

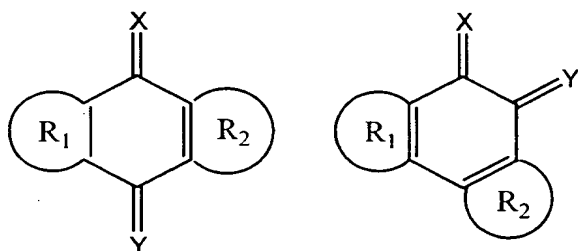
25 However, the thickness of the reaction layer is not solely a function of the dry thickness of the working electrode but also depends upon the effect of the sample on the working electrode. In the case of aqueous samples the formulation of the working electrode ingredients will effect the degree of water uptake this layer displays.

Claims:

1. A single use disposable electrode strip for attachment to the signal readout circuitry of a sensor system to detect a current representative of an analyte in an aqueous sample, the strip comprising:

- a) an elongated support having a substantially flat, planar surface, adapted for releasable attachment to said readout circuitry;
- b) a first conductor extending along said surface and comprising a conductive element for connection to said readout circuitry;

an active electrode on said surface in contact with said first conductor, said active electrode comprising a nicotinamide cofactor-dependent enzyme, a nicotinamide cofactor, and a mediator compound having one of the following two formulae:



where X and Y can independently be oxygen, sulphur, CR^3R^4 , NR^3 , or NR^3R^{4+} or the functional group CZ^1Z^2 , where Z^1 and Z^2 are electron withdrawing groups; R_1 and R_2 can independently be a substituted or unsubstituted aromatic or heteroaromatic group; and R^3 and R^4 can independently be a hydrogen atom, a hydroxyl group or a substituted or unsubstituted alkyl, aryl, heteroaryl, amino, alkoxyl, or aryloxyl group,

wherein said active electrode is formulated with filler and binder ingredients such that said electrode gives a

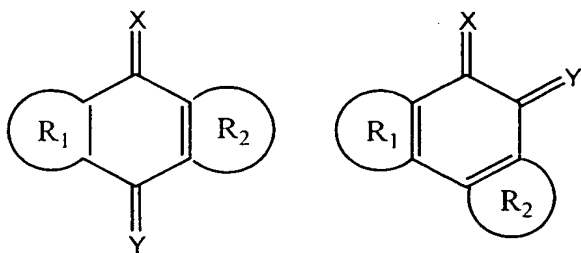
monotonic response to concentrations of said analyte
between about 1 and 8 mM when measurement is made in a
kinetic mode in which simultaneous oxidation and
reduction of the mediator occurs during the measurement;

- 5 c) a second conductor extending along said surface,
 comprising a conductive element for connection to
 said readout circuitry;
- d) a reference/counter electrode in contact with said
 second conductor;
- 10 e) said conductors being spaced apart so as not to be
 in electrical contact and being configured so as not
 to be brought into electrical contact when said
 aqueous sample is placed on said strip;
- f) said active electrode and said reference/counter
15 electrode being configured so that both may be
 simultaneously covered by a small drop of said
 aqueous sample to provide an electrical
 conduction path between said electrodes.

2. A process of measuring the concentration in an aqueous sample of an analyte subject to oxidation by a NAD(P)^+ dependent enzyme comprising

- a) oxidizing the analyte with the NAD(P)^+ dependent enzyme in the presence of NAD(P)^+ ;

oxidizing the NAD(P)H generated by reaction with the analyte and NAD(P)^+ dependent enzyme with a mediator compound having one of the following two formulae:



where X and Y can independently be oxygen, sulphur, CR^3R^4 , NR^3 , or NR^3R^{4+} or the functional group CZ^1Z^2 , where Z^1 and Z^2 are electron withdrawing groups; R_1 and R_2 can independently be a substituted or unsubstituted aromatic or heteroaromatic group; and R^3 and R^4 can independently be a hydrogen atom, a hydroxyl group or a substituted or unsubstituted alkyl, aryl, heteroaryl, amino, alkoxyl, or aryloxyl group; and



- b) applying an electrical potential at an electrode to reoxidize the mediator compound reduced in oxidizing NAD(P)H and observing the resultant current,

wherein some of the mediator compound is being reduced by reaction with NAD(P)H while some of the mediator compound is being oxidized by transfer of electrons to said electrode during a measurement period and the rate of oxidation of the mediator compound over said measurement period and consequently the resultant observed current is monotonically related to the concentration of analyte in the sample.

3. The process of Claim 2 wherein the NAD(P)^+ dependent enzyme, NAD(P)^- and mediator compound have been applied to the surface of said electrode in combination with a binder and a filler.
4. The process of Claim 3 wherein the current observed during the measurement
- 5 period is linearly related to the concentration of the analyte in the sample.
5. The electrode strip of Claim 1 wherein the mediator compound is 1, 10-phenanthroline quinone.
6. The electrode strip of Claim 5 wherein the cofactor-dependent enzyme is Glucose Dehydrogenase.
- 10 7. The electrode strip of Claim 5 wherein the cofactor-dependent enzyme is 3-Hydroxybutyrate Dehydrogenase.
8. The process of Claim 2 wherein the mediator component is 1, 10-phenanthroline quinone.
9. The process of Claim 8 wherein the cofactor-dependent enzyme is Glucose
- 15 Dehydrogenase.
10. The process of Claim 8 wherein the cofactor dependent enzyme is 3-Hydroxybutyrate Dehydrogenase.
11. The process of Claim 2 wherein the applied potential is 200 mV or less.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1467/GM/ms		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/21815	International filing date (day/month/year) 16/10/1998	Priority date (day/month/year) 16/10/1997	
International Patent Classification (IPC) or national classification and IPC C12Q1/00			
Applicant ABBOTT LABORATORIES et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 7 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input type="checkbox"/> Certain documents citedVII <input checked="" type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 20/04/1999		Date of completion of this report 25. 01. 00	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Thiele, U Telephone No. +49 89 2399 8643 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/21815

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-5,8-16,18-29 as originally filed

6,7,17 as received on 10/11/1999 with letter of 04/11/1999

Claims, No.:

1-11 as received on 10/11/1999 with letter of 04/11/1999

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/21815

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-11
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 1-11
Industrial applicability (IA)	Yes: Claims 1-11
	No: Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V

- 1) Reference is made to the following documents

D1 BIOSENSORS & BIOELECTRONICS, vol. 11, no. 12, 1996, pages 1267-1275 (cited in the application on page 19)

D2 Derwent WPI AN 95-330848 [43] & JP-A-07 209 243

D3 US-A-5 212 622

- 2) The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claim 1 does not involve an inventive step (Rule 65(1)(2) PCT).

The closest state of the art is considered to result from D1. This document shows cyclic voltametry with a conventional electrochemical cell using a reference an a counter electrode, and a NADH sensor. The latter electrode is construed by drop coating with polyethylene oxide as a matrix for glucose oxidase, the nicotinamide cofactor and 1,7-, respectively 1,10-phenanthroline-5,6-dione as mediator (see esp. page 1269; Fig. 2).

The subject-matter of claim 1 is distinguished therefrom by the following features (see also page 19, lines 17 - 22):

- "the active electrode is formulated with filler and binder ingredients such that said electrode gives monotonic response to concentrations of said analyte between about 1 and 8 mM when measurement is made in a kinetic mode in which simultaneous oxidation and reduction of the mediator occurs during the measurement"
- the specific configuration identified in items e) and f) of claim 1

These distinguishing features result in a stable reaction layer (see page 19, lines 17 et seq.).

It is noted that according to the applicant, the present invention was based on the

discovery of NAD and NADP mediator compounds that do not bind irreversibly to thiol groups in the active sites of intracellular dehydrogenase enzymes. In the light of D1, however, this view cannot be accepted.

The objective technical problem to be solved by the invention was therefore in the light of the above argumentation to increase the stability of the reaction layer on a biosensor electrode.

The person skilled in the art would turn to document D3. This document is concerned with the same problem, that is provision of material which remains intact during use in aqueous media (see col. 1, lines 53 - 61). It is there suggested to solve the problem by using filler and binder materials (see col. 2, line 61 - col. 4, line 11). This suggestion essentially corresponds to the features which distinguish the subject-matter of claim 1 from the art.

The further distinguishing features would appear to merely be slight constructional changes in the sensor system of D1 which come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen (see also D2).

Consequently, the subject-matter of claim 1 lacks an inventive step.

- 3) The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claim 5 does not involve an inventive step (Rule 65(1)(2) PCT).

The process of claim 5 would automatically exist whenever the non-inventive device according to claim 1 is used. Consequently, analogous objections as regards inventiveness apply.

- 4) Dependent claims 2 -4 and 6 - 11 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Art. 33(3) PCT).

The subject-matter of said claims would not appear to solve, within the disclosure

of the present application, a technical problem in an unexpected way.

Section VII

- 1) The incorporation of prior art by reference is not allowed as the international application should be self-contained (see further Guidelines, C-II, 4.17). Phrases such as "and incorporated by reference ..." to be found e.g. on page 7 contravene said requirement.

Section VIII

- 1) Claims 1, 2 and 4 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the subject-matter in terms of the result to be achieved ("wherein said active electrode is formulated [...] such that [...] occurs during measurement"; "wherein some mediator compound is reduced [...] and consequently the resultant observed current is monotonically related to [...]"; claim 4 in its entirety). Such a definition is only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, such a formulation is not allowable because it seems possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved.
- 2) The vague and imprecise statement in the description on page 29 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the Guidelines, C-III, 4.3a).
- 3) The embodiment of the invention described on page 7, lines 1 - 4 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 6237.PC.01	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 21815	International filing date (day/month/year) 16/10/1998	(Earliest) Priority Date (day/month/year) 16/10/1997
Applicant ABBOTT LABORATORIES et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

2

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/21815

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/00 G01N27/30 G01N27/327

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GENG, L. ET AL.: "Amperometric biosensors based on dehydrogenase/NAD and heterocyclic quinones" BIOSENSORS & BIOELECTRONICS, vol. 11, no. 12, 1996, pages 1267-1275, XP002095074 cited in the application see the whole document ---	1-11
A	ECKERT, T. S. ET AL.: "Chemical Properties of Phenanthrolinequinones and the Mechanism of Amine Oxidation by o-Quinones of Medium Redox Potentials" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 105, 1983, pages 4431-4441, XP002095436 see the whole document --- -/--	1-11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 March 1999

Date of mailing of the international search report

16/03/1999

Name and mailing address of the ISA

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Authorized officer

Gundlach, B

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/21815

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 188 728 A (CRANFIELD INST OF TECHNOLOGY T) 7 October 1987 see abstract see page 1, line 56 - page 2, line 5 see page 3, line 1 - line 17 ---	1,2,5,6, 8,9,11
A	US 4 758 323 A (DAVIS GRAHAM ET AL) 19 July 1988 see abstract; example 3 ---	1-4,6,7, 11
A	EP 0 125 867 A (GENETICS INT INC) 21 November 1984 cited in the application see abstract ---	1,2
A	EP 0 794 429 A (MATSUSHITA ELECTRIC IND CO LTD) 10 September 1997 see abstract; figures 1,2 see page 2, line 9 - line 22; example 2 see page 3, line 53 - page 4, line 25 see page 4, line 59 - page 5, line 9 ---	1-5,8
A	US 5 628 890 A (CARTER NIGEL F ET AL) 13 May 1997 see figure 1 -----	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/21815

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2188728	A	07-10-1987	NONE	
US 4758323	A	19-07-1988	AU 564494 B	13-08-1987
			AU 2775184 A	31-01-1985
			AU 564495 B	13-08-1987
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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Date of mailing (day/month/year) 16 June 1999 (16.06.99)	Applicant's or agent's file reference 6237.PC.01
International application No. PCT/US98/21815	Priority date (day/month/year) 16 October 1997 (16.10.97)
International filing date (day/month/year) 16 October 1998 (16.10.98)	
Applicant FORROW, Nigel, J. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12Q1/00 G01N27/30 G01N27/327

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

3 March 1999

Date of mailing of the international search report

16/03/1999

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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